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Review

Current biomarkers of invasive sporadic pituitary adenomas

Biomarqueurs actuels des adénomes hypophysaires sporadiques invasifs

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Abstract

Though pituitary adenomas (PA) are considered benign, some of them exhibit invasive behaviors such as recurrence and low rate of total surgical resection. Reliable prognostic biomarkers for invasive PA are highly desired; however they remain to be identified. In this review, we summarize the current controversial findings of biomarkers for invasive sporadic PA, and we discuss the possible reasons for the controversies.

Keywords: Pituitary adenoma; Biomarkers; Invasiveness

Résumé

Bien que les adénomes hypophysaires (AH) soient considérés comme bénins, certains d'entre eux présentent des comportements invasifs tels la récidive et le faible taux de résection chirurgicale totale. La recherche de biomarqueurs pronostiques fiables des adénomes hypophysaires invasifs est très active. Dans cette revue, nous résumons les conclusions actuelles sur les biomarqueurs de AH sporadiques invasifs et discutons des raisons possibles des controverses associées.

Mots clés : Adénome hypophysaire ; Biomarqueurs ; Invasivité

1. Introduction

Pituitary adenomas (PA) are typical benign tumors of the sellar region. The prevalence of PA is approximately 17%, accounting for about 15% of intracranial tumors [1]. PAs causes significant morbidity because of expanding size, hemorrhage, invasion to surrounding structures, and/or inappropriate pituitary hormone expression [2]. Some PAs can infiltrate the adjacent structures, such as the sphenoid sinus, the cavernous sinuses, the bony parts of the sella turcica, the dura mater, the nervous tissue, and even the fourth cerebral ventricle and the hypothalamus. These behaviors of PA are defined as "invasion". Nearly 44.2% of PAs are invasive [3]. Two classification systems are used to characterize PAs. One is the Hardy classification system [4]. The other one is Knosp classification system [5]. Grade III (localized sellar destruction) and grade IV (diffuse destruction) in Hardy classification system and Grade III (tumor extends laterally to the internal carotid artery within the cavernous sinus) and Grade IV (total encasement of the intracavernous carotid artery) in Knosp classification system are defined "invasive".

When evaluating PAs, the terminology "aggressive" has been used as the synonyms for "invasive" [6]. But the classical definition of aggressive PAs includes not only a massive invasion of the surrounding anatomical structures but also a high risk of recurrence [6,7]. The 2004 World Health Organization (WHO) classification of pituitary tumors is typical pituitary adenoma, atypical pituitary adenoma and pituitary carcinoma. Atypical PAs are defined as follows: MIB-1 proliferative index greater

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than 3%, excessive p53 immunoreactivity, and increased mitotic activity [8]. Atypical PAs exhibit highly invasive manifestations, 83% of which demonstrate invasion on MR imaging [9]. PAs can be invasive upward, downward and laterally. Upward is the most frequent, and tumor may penetrate and destroy the covering diaphragm sellae, get to the suprasellar space, and infiltrate surrounding tissues, which may compress and damage the chiasm, hypothalamus and optic nerves, and indent the floor of the third ventricle [10]. Downward invasion of PAs is less common, it involves the sphenoid bone, dura and sinus. Lateral invasion into the cavernous sinus is least common because of the bone and connective tissue of sella [10].

Invasive PAs are related to significant morbidity, poor prognosis, and poor response to the different alternatives therapies. Surgery is considered to be the best treatment to invasive PAs that can be conducted transsphenoidally, transcranially or a combination of both. But prolactinomas is an exception [7]. Surgery can achieve local control completely or partly and release compression of vital structures. Due to the infiltration to the adjacent structures, tumor tissues can be residual, which may augment hormone values and lead to the need for repeated surgeries or pharmacological treatment. Dopamine agonists and somatostatin analogs are the most widely used to treat PAs. But part of patients with invasive PAs can be drug resistance at the beginning or develop to be resistant to these drugs [11]. When surgery and pharmacotherapy failed, radiotherapy is used as the third-line therapy [7]. In conclusion, the prognosis of invasive PAs is poor and the therapeutic options are limited.

A series of biomarkers for invasive PAs have been investigated. These markers belong to a wide range of biological domains including chromosomal alterations, oncogenes, tumor suppressor genes, proliferation markers, growth factors and their receptors, factors related to angiogenesis or cell adhesion and specific molecules in peripheral blood [6]. But no single biological marker has been found to predict invasion of PAs independently. In fact, different studies may get opposite results. This review will list as much biological markers of the invasive PAs as possible, and try to find the factors which mostly result in the opposite results of some specific biomarkers.

2. Biomarkers of invasive pituitary adenomas

Early diagnosis and prediction of invasive PAs before "invasion" are valuable. The so called "biomarkers" of invasive PAs can be on the one hand useful for prediction of biological behavior thus we can choose appropriate therapeutic regimen at early stage of this disease, on the other hand may be important factors leading to the invasion which can be targets for drugs.

Invasive PAs are closely associated with clinical features. Macroadenomas are more likely than microadenomas to be invasive [10]. Among all the functioning tumors, silent corticotrope adenomas show the highest frequency of gross invasion, TSH-producing adenomas are less. Following are GH-, PRL-, ACTH-producing adenomas, even more in null cell adenomas. FSH/LH-producing adenomas show the least frequency [12]. There is no concrete data show that invasion of PAs is related with age and gender.

3. Cell proliferation

Cell proliferation has been widely studied and accepted to be an important factor, which causes the different biological behavior of the invasive and non-invasive PAs. Cell cycle-related proteins can reflect cell proliferation effectively. Among these proteins, Ki-67, which expressed during the G1, S, G2 phases of cell division, is most widely studied by MIB-1 immunoassaying. MIB-1 proliferative index is even used in the classification of PAs of 2004 WHO [8]. But results of different studies may not be consistent (Table 1). In Table 1, we list 28 studies which involve Ki-67, and we also list the hormonal types and the sample size of each study. In most studies, Ki-67 is not the key investigated factor which is used to identify the relation between key investigated factors and proliferation. The results of 18 studies show Ki-67 expressed more in invasive adenomas while other 10 studies show no correlation. The reasons for this opposite conclusion are complicated, different sample sizes and/or types of PAs may be two of the reasons.

A subunit of the DNA polymerase-δ holoenzyme proliferating nuclear cell antigen (PCNA) is another important cell cycle-related protein, which synthesized in the late G_1 and S phases [13]. PCNA is not associated with pituitary adenoma invasion in most studies [14–17], but also increased in few studies [18,19]. This indicates that Ki-67 is a more sensitive factor than PCNA to assess the proliferative difference between the invasive and non-invasive PAs.

Topoisomerase IIα (Topo IIα) is another key enzyme expressed in cell cycle progression and also regarded as a cell proliferation marker [20]. Vidal's study [21] shows the expression of Topo IIα is increased in invasive PAs, but Wolfsberger et al. found no difference [22].

These results indicate that Ki-67 may be the best factor, which reflects the cell proliferation of invasive proliferation state even though the conclusion is not consistent.

4. Chromosome and genes

Abnormalities of chromosome, oncogenes and anti-oncogenes play an important role in tumor initiation and local progression. In invasive PAs, chromosome 9, 11, 19 numeric alterations is more than non-invasive ones [43]. Also, loss of heterozygosity (LOH) of 11q13, 13q12-14, 10q26 were frequently found in invasive PAs [44–46]. The imbalance of oncogenes and anti-oncogenes takes part in the initiation of tumor, and some of them relate to further malignant behavior [47]. Among all the oncogenes and anti-oncogenes, p53 may be the most studied one. Excessive p53 immunoreactivity is a major part of criteria of "atypical adenoma" according to 2004 WHO classification [8], but the inconsistent conclusions also exist (see Table 2). It seems that the relation between p53 and invasion is not that close, and Oliveira et al. found the p53 positive rate is only 1.3% in 148 cases of PAs, thus considered it inadequate as a routine marker for invasive behavior [48]. Changes of other oncogenes or anti-oncogenes such as Ras, p16,RB,p27,11p,nm23 also induces invasion of adenomas [33,49,45,50–52]. Changes of other genes such as point mutation of PKC [53], mutations of P13 K [54] are

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